REMARKS & CONCLUSION

The above-listed claim amendments along with the following remarks are fully responsive to the Office Action of January 13, 2006. Claims 1-62 are pending. The Action withdrew from consideration claims 5-8 and 51-62 as being drawn to a non-elected invention. Claims 1, 9-12, 14, 18-21, 23-28, 31, 36-49 are amended either to correct typographical errors or to comply with claim 1 as amended. Claims 16 and 35 are canceled. By this Amendment, claims 1-4, 9-15, 17-34 and 36-50 are currently under consideration.

Species Election

Applicants would like to thank the Examiner for withdrawing the species election.

Claim Amendments

Claim 1 is amended to recite an immunoconjugate that comprises an antibody, a chemotherapeutic moiety and a linker comprising a thiol-reactive functional group for binding to the antibody via a thiol group, a water-solubilizing moiety and the chemotherapeutic moiety attached via an intracellularly-cleavable moiety other than a hydrazone. No new matter is added by this amendment. Support for this amendment may be found throughout the specification and claims as originally filed and at least at paragraphs [0075], [0076] and [0080].

Claim 14 is amended to include a polyethylene glycol (PEG) residue. No new matter is added by this amendment. Support for this amendment may be found at least at paragraph [0076] and Example 3.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claim 32 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Office Action stated that neither the specification nor the claims appear to identify what "R" could be in claim 32. Paragraph [0046] of the present application identifies that "R is the side chain of any amino acid" in the linker. The "R" that is described at paragraph [0046] pertains to the "R" that is disclosed in the linker recited in claim 32. Applicants request withdrawal of this rejection.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Claims 1-4, 9-15, 27-34 and 48-50 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action asserts that "the claims are inclusive of a genus of targeting moieties. However, the written description in this case only sets forth one species of targeting moieties, wherein the targeting moiety is an antibody." [Office Action, page 3]

Claim 1 is amended to recite that the immunoconjugate comprises "an antibody." This amendment should satisfy the written description requirement. Support for this amendment can be found throughout the Specification and claims as originally filed and at least at paragraphs [0035], [0036], [0052]-[0055] and Examples 4-8. Moreover, the Office Action indicated that "only one species of targeting moieties, wherein the targeting moiety is an antibody, but not the full breadth of claims, meets the written description provision of 35 U.S.C. §112, first paragraph." [Office Action, page 5]

Applicants are clearly in possession of the invention as of the filing date of the application. Therefore, Applicants respectfully request withdrawal of this rejection.

Claim Rejections – 35 U.S.C. § 102

Claims 1-3, 9-10, 16-7, 21-22, 24 and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Abrams *et al.* (US Patent 5,112,954). Abrams is cited as teaching "an immunoconjugate comprising a targeting entity attached to a cytotoxic agent, wherein the targeting entities include, but are not limited to, hormones or antibodies." Abrams is further cited as teaching that "the targeting entity and cytotoxic agent are attached via a linker, wherein a free thiol group present on the targeting entity may be reacted with an activated double bond...to produce a thioether bond. [Office Action, page 5-6]

Claims 1-4, 9, 11, 16-17, 19, 21-23, 27-29, 33, 35-36, 38, 40-42 and 48-49 are rejected under 35 U.S.C. § 102(b) as being anticipated by Chari *et al.* (WO 01/24763 A2, 2001). Chari is cited as teaching an immunoconjugate comprising a cell binding agent (that may include an monoclonal antibody) and at least one therapeutic agent (that may include an anti-mitotic agent). The cell binding agent is linked to the therapeutic agent via a linking group. The monoclonal antibody is linked via a thiol group and the therapeutic agent is linked via a ester linkage.

Rejections under 35 U.S.C. §102 are improper unless each and every element of the claimed subject matter is disclosed in a single prior art reference. Applicants submit that neither references, Abrams nor Chari, disclose each and every element of amended claim 1, namely, neither, Abrams nor Chari disclose "an immunoconjugate that comprises an antibody, a chemotherapeutic moiety, and a linker comprising a thiol-reactive functional group for binding to the antibody via a thiol group, a water-solubilizing moiety, and the chemotherapeutic moiety attached via an intracellularly-cleavable moiety other than a hydrazone. Therefore, Applicants respectfully request the withdrawal of this rejection.

Claim Rejections – 35 U.S.C. § 103

Claims 15 and 34 .are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chari *et al.* in further view of Voegelein *et al.* (J. Med. Chem. 1991; 34:992-998) or Bennouna *et al.* (Int. J. Clin. Oncol. 2002; 7:236-244) or Perez *et al.* (European Journal of Pharmacology 1998; 356:239-243).

Chari does not make obvious claims 15 and 34 because Chari does not teach or suggest "an immunoconjugate that comprises an antibody, a chemotherapeutic moiety and a linker comprising a thiol-reactive functional group for binding to the antibody via a thiol group, a water-solubilizing moiety and the chemotherapeutic moiety attached via an intracellularly-cleavable moiety other than a hydrazone," as recited in amended claim 1. In fact, the Office Action acknowledges that "[t]he combination of Chari *et al.* with Voegelein *et al.* or Bennouna *et al.* or Perez *et al.* does not explicitly teach that the linker further comprises a water-solubilizing moiety between the therapeutic moiety and the cell binding agent." Furthermore, the Office Action acknowledged that "Chari *et al.* does not explicitly teach that the anti-mitotic agent is a taxane, doxorubicin and /or analog thereof, or camptothecin, e.g. CPT, and /or analog thereof." [Office Action at pg. 8]

A *prima facie* case of obviousness requires: 1) the prior art reference or references must teach or suggest all the claim limitations, (2) some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or combine the teachings; and (3) a reasonable expectation of success. [MPEP 2143] Chari *et al.* fails to establish a *prima facie* case of obviousness, because at a minimum it neither teaches nor suggests a linker that includes a water-solubilizing moiety.

This deficiency is not corrected by any of the other cited references, either alone or in combination. There is no disclosure in any of the other cited art, nor does the Office Action point to any disclosure in the cited references of Voegelein *et al.*, Bennouna *et al.* or Perez *et al.* that discloses this element of the claimed subject matter, namely a linker that includes a solubilizing moiety.

"Combing prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight." *In re* Dembiczak, 175 F. 3d 994, 50 USPQ2d (Fed. Cir. 1999). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 12-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chari *et al.* in combination with Voegelein *et al.*, Bennouna *et al.* or Perez *et al.* in further view of Li *et al.* (2001/0034363, 2001) and Miller *et al.* (24th ACS National Meeting, August 18-22, 2002, Boston, Mass., Poster Presentation).

Chari, Voegelein, Bennouna and Perez were cited as discussed in response to the previous rejection. Li was cited as teaching paclitaxel conjugated to water-soluble metal chelators. Miller was cited as teaching the development of Taxoid derivatives with enhanced toxicity and solubility.

As discussed in response to the previous rejection, Chari and the combination of references does not make obvious the claims on which claims 12 and 14 depend. Moreover, Li does not make up for the deficiency of the primary combination.

Li does not teach or suggest a targeted delivery for drugs using antibodies, as recited in amended claim 1. Rather, Li teaches how to solubilize insoluble drugs for systemic use. There is not motivation for one skilled in the art to combine Chari with Voegelein *et al.*, Bennouna *et al.* or Perez *et al.* in view of Li because, as discussed above, Chari does not teach or suggest including a water-solubilizing moiety in the linker and Li does not teach targeted delivery of drugs.

Miller *et al.* is cited as providing the requisite motivation to combine Chari with Voegelein *et al.*, Bennouna *et al.* or Perez *et al.* in view of Li because Miller notes that "one problem associated with antibody-drug formation is the presence of free drug found in the conjugate as a result of hydrophobic interactions that cause the drug to 'stick' to the antibody such that it compromises the efficiency of the antibody."

Miller *et al.* do not offer evidence that introducing water solubilizing groups solved the "sticking" problem. As a matter of fact, self association or "stacking" of drugs is a well known problem even when using highly soluble drugs such as doxorubicin and daunorubicin, or other entities such as proflavin, purine derivatives, and acridine orange. Moreover, free drug from antibody-drug conjugates can be removed by ion-exchange chromatography. Miller's assertion that solubilization would remedy 'sticking' of free drugs is unsubstantiated and without merit and in fact Miller indicates that "as the size of the PEG was increased there was a large increase in water solubility, but this was unfortunately accompanied by a decrease in cytotoxicity." Thus, Miller does not provide a motivation to make the combination, nor the expectation of success upon doing so.

Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 25 and 44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chari *et al.* in view of Newton *et al.* (Blood 2001, 97:528-535).

As discussed above, Chari does not make obvious the claims on which claims 25 and 44 depend. Because Newtown does not make up for the deficiencies of Chari, claims 25 and 44 are not obvious for the same reasons as the base claims on which they depend. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

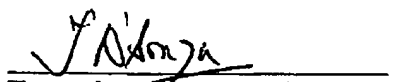
Claims 18, 20, 26, 37, 39, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari *et al.* combined with Newton *et al.* in view of Cao *et al.* (Bioconjugate Chemistry 1998; 9:635-643).

As discussed above, Chari does not make obvious the claims on which claims 18, 20, 26, 37, 39, 45 and 47 depend. Because Newton does not make up for the deficiencies of Chari, claims 25 18, 20, 26, 37, 39, 45 and 47 are not obvious for the same reasons as the base claims on which they depend. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

Conclusion

In light of the amendments and remarks herein, Applicants respectfully request entry of the paper. If there are any remaining questions, the Examiner is requested to contact the undersigned at the number listed below.

Respectfully Submitted,



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